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10/593,103	09/15/2006	Yukihiko Mashima	Q96480	9096

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EXAMINER	
SHAW, AMANDA MARIE	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,103	MASHIMA, YUKIHIKO	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1,7-12 and 14-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/15/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/2008, 9/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-39 are currently pending.

Applicant's election without traverse of Group II in the reply filed on June 24, 2009 is acknowledged. Additionally Applicants elected the following polymorphisms for examination: 1105 T>C polymorphism of the myocilin gene (Phe369Leu), 412G>A polymorphism of the optineurin gene, and CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln).

Claims 17-12, 14-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 24, 2009.

2. In view of the submission filed on June 24, 2009 this application is now in compliance with the sequences rules.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 60/553,986, 60/604,704, and 60/607,359, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. In the instant case the prior filed applications do not disclose a method of diagnosing or predicting susceptibility to optic neuropathy by genotyping the noelin-2 gene. Further the prior filed applications do not teaches that CGG to CAG substitution at codon 144 of the noelin-2 gene. As such the priority date for this application is March 18, 2005 which is based on the filing date of PCT/JP2005/005601.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6 and 13 are indefinite because the claims require determining the genotype of the sample with respect to a set of polymorphisms comprising: 1105 T>C polymorphism of the myocilin gene (Phe369Leu), 412G>A polymorphism of the optineurin gene, and CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln) and diagnosing or predicting susceptibility to optic neuropathy/glaucoma based on the genotype. First of all in view of the phrase "genotype with respect to" its not clear if the claims actually require that the genotype consists of the set of recited polymorphisms themselves or if this could refer to determining the genotype of polymorphisms related to or in linkage disequilibrium with the recited polymorphisms. If the claims were limited to actually detecting the recited polymorphisms themselves then it would be unclear if all three of the polymorphisms have be present in order to make the diagnosis or predict susceptibility or if the presence of any combination of one, two, or three polymorphisms of the polymorphisms in the set have to be present in order to make the diagnosis or predict susceptibility. Although the claims require genotyping with respect to three polymorphisms the claims do not actually require that all three of them have to be present in order to make the diagnosis or predict susceptibility.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-6 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing or predicting susceptibility to primary open angle glaucoma in a human subject comprising the steps of: (i) obtaining a biological sample from the subject, (ii) testing the biological sample to identify the nucleotide present at position 462 of the noelin 2 gene, the nucleotide present at position 1105 of the myocilin gene, and the nucleotide present at position 412 of the optineurin gene, and (iii) determining that the subject has or is susceptible to having primary open angle glaucoma wherein any of the following nucleotides are present: the A nucleotide at position 462 of the noelin 2 gene, the C nucleotide at position 1105 of the myocilin gene, or the A nucleotide at position 412 of the optineurin gene, does not reasonably provide enablement for a method of diagnosing or predicting susceptibility to any type of optic neuropathy, any type of glaucoma, or Leber's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

The claims are drawn to a method for diagnosing or predicting susceptibility to optic neuropathy (such as glaucoma) in a human subject. The claims require genotyping a sample obtained from a human subject for a set of polymorphisms comprising: 1105 T>C polymorphism of the myocilin gene (Phe369Leu), 412G>A polymorphism of the optineurin gene, and CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln). The nature of the invention requires a reliable association between these polymorphisms and optic neuropathy. This invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Scope of the Claims:

Claim 2 is drawn to a method for diagnosing or predicting susceptibility to optic neuropathy in a human subject. The phrase "optic neuropathy" encompasses any type of damage to the optic nerve due to any cause (i.e., glaucoma, Leber's disease, lupus, multiple sclerosis). The claims require genotyping a sample obtained from the subject for a set of polymorphisms and diagnosing or predicting susceptibility to optic neuropathy in the subject based on the genotype. The claims encompass a method wherein the presence of any combination of one, two, or three polymorphisms selected from: 1105 T>C polymorphism of the myocilin gene (Phe369Leu), 412G>A polymorphism of the optineurin gene, and CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln) is indicative of having or being susceptible to optic neuropathy because although the claims require genotyping to determine if all three

polymorphisms are present the claims do not actually require that all three of them have to be present in order to make the diagnosis or predict susceptibility. Claim 3 is limited to a method wherein the optic neuropathy is glaucoma or Leber's disease.

Claim 5 is drawn to a method for diagnosing or predicting susceptibility to glaucoma. The term "glaucoma" encompasses any disease that affects the optic nerve and involves a loss of retinal ganglion cells (i.e., primary open angle glaucoma, primary angle closure glaucoma, primary congenital glaucoma, phacogenic glaucoma, etc). The claims require genotyping a sample obtained from the subject for a set of polymorphisms and diagnosing or predicting susceptibility to glaucoma in the subject based on the genotype. The claims encompass a method wherein the presence of any combination of one, two, or three polymorphisms selected from: 1105 T>C polymorphism of the myocilin gene (Phe369Leu), 412G>A polymorphism of the optineurin gene, and CGG to CAG substitution at codon 114 of the noelin 2 gene (Arg144Gln) is indicative of having or being susceptible to glaucoma because although the claims require genotyping to determine if all three polymorphism are present the claims do not actually require that all three of them have to be present in order to make the diagnosis or predict susceptibility.

Teachings in the Specification and Examples:

Example 5 in the specification discusses a novel myocilin (MYOC) gene mutation, PHe369Leu, found in Japanese patients with primary open angle glaucoma (POAG). Blood samples were taken from 171 POAG patients and 100 normal subjects. Genomic DNA was isolated from the blood samples and seven exons of the MYOC

gene were amplified by PCR. Then the PCR products were injected into a chromatograph for analysis using the WAVE System for DHPLC analysis. When abnormal chromatographic patterns were detected the sample that showed the abnormal chromatographic pattern was sequenced using the ABI310 automated sequencer. Four glaucoma causing mutations were identified in 5 of 171 patients with POAG (See Table 12). The 1105T>C polymorphism (Phe369Leu) was detected in 1/171 POAG patients. This mutation was not present in any of the 100 controls.

Example 6 in the specification discusses variants in the optineurin (OPTN) gene in Japanese patients with glaucoma. Blood samples were taken from 194 POAG patients, 217 normal tension glaucoma (NTG) patients and 218 normal subjects. Here it is noted that NTG comprises one third of POAG and thus is considered a subset of POAG. Genomic DNA was isolated from the blood samples and 13 exons of the OPTN gene were amplified by PCR. Then the PCR products were injected into a chromatograph for analysis using the WAVE System for DHPLC analysis. When abnormal chromatographic patterns were detected the sample that showed the abnormal chromatographic pattern was sequenced using the ABI310 automated sequencer. Seventeen sequence changes were identified in the glaucoma patients and control subjects (See Table 14). The 412 G>A polymorphism (Thr34Thr) was present in 69/201 patients with POAG, 74/232 patients with NTG, and 52/218 controls. The Thr34Thr polymorphism was significantly associated with POAG and NTG (Table 15). A significant association was found in patients with POAG ($p=0.009$ in genotype frequency: GG vs. GA and AA, and $p=0.003$ in allele frequency).

Example 12 in the specification discusses variants in the noelin 2 gene in Japanese patients with open angle glaucoma. Blood samples were taken from 276 POAG patients, 340 NTG patients and 300 normal subjects. Here it is noted that NTG comprises one third of POAG and thus is considered a subset of POAG. Genomic DNA was isolated from the blood samples and 6 exons of the noelin 2 gene were amplified by PCR. Then the PCR products were injected into a chromatograph for analysis using the WAVE System for DHPLC analysis. When abnormal chromatographic patterns were detected the sample that showed the abnormal chromatographic pattern was sequenced using the ABI310 automated sequencer. Ten sequence changes were identified in the glaucoma patients and control subjects (See Table 42). The CGG to CAG substitution at codon 144 (Arg144Gln) was detected in 1/276 POAG patients, 1/340 NTG patients, and 0/300 controls.

Accordingly, the specification is enabled for a method for diagnosing or predicting susceptibility to primary open angle glaucoma in a human subject comprising the steps of: (i) obtaining a biological sample from the subject, (ii) testing the biological sample to identify the nucleotide present at position 462 of the noelin 2 gene, the nucleotide present at position 1105 of the myocilin gene, and the nucleotide present at position 412 of the optineurin gene, and (iii) determining that the subject has or is susceptible to having primary open angle glaucoma wherein any of the following nucleotides are present: the A nucleotide at position 462 of the noelin 2 gene, the C nucleotide at position 1105 of the myocilin gene, or the A nucleotide at position 412 of the optineurin gene.

The specification does not provide support for a method of diagnosing or predicting susceptibility to any type of optic neuropathy, any type of glaucoma, or Leber's disease because the teachings in the specification are limited to an association between the three claimed polymorphisms and primary open angle glaucoma.

The Predictability or Unpredictability of the Art:

In the instant case it is highly unpredictable as to whether the results obtained with POAG can be extrapolated to other types of optic neuropathy, specifically other types of glaucoma. Optic neuropathies are known to be a genetically and clinically heterogeneous group of disorders. The teachings in the specification are limited to an association between the 3 mutations and the occurrence of POAG. There are no teachings in the specification regarding the frequency of these mutations in other forms of optic neuropathy. Accordingly, it is unpredictable as to whether the presently claimed method can be used to diagnose or predict susceptibility to any type of optic neuropathy.

Quantity of Experimentation Necessary:

The specification teaches 3 polymorphisms that are associated with primary open angle glaucoma. To determine it these polymorphisms can be used to diagnose or predict susceptibility to other types of optic neuropathies would require extensive experimentation. For example, such experimentation may involve sequencing the MYOC, OPTN, and noelin-2 genes of affected individuals having a representative number of different types of optic neuropathy and then determining if the 3 claimed polymorphisms are present in other types of optic neuropathies and whether or not they

can be used diagnostically. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not provide support for a method of diagnosing or predicting susceptibility to any type of optic neuropathy, any type of glaucoma, or Leber's disease. The teachings in the specification are limited to an association between the three claimed polymorphisms and primary open angle glaucoma. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the

unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-6 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa (J. Glaucoma 2004) in view of Umeda (Invest Ophthalmol Vis Sci 2003) and Mukhopadhyay (Molecular Vision 2004).

Ishikawa teaches a method wherein blood samples were collected from 171 primary open angle glaucoma (POAG) patients and 100 normal subjects. Genomic DNA was isolated from the blood samples and the 7 exonic regions of the MYOC gene were amplified by PCR. One missense mutation Phe369Leu was found to be associated with adult onset POAG (abstract). As such Ishikawa teaches a method comprising obtaining a biological sample from a subject and determining the genotype of the sample with respect to the 1105 T>C polymorphism of the MYOC gene (PHE369Leu). Ishikawa further teaches that early diagnosis is critical because early treatment can postpone or prevent loss of vision. Thus information identifying a genetic risk of developing the disease would permit individuals carrying glaucoma causing

mutations to undergo regular examinations to identify and treat POAG at an early stage (page 469, col 2). As such Ishikawa teaches diagnosing or predicting susceptibility to optic neuropathy based on genotyping. Further Ishikawa teaches that they identified three other glaucoma causing mutations, namely Ile360Asn, Ala363Thr, and Thr448Pro).

Ishikawa does not teach a method comprising determining the genotype of the sample with respect to the 412G>A polymorphism of the OPTN gene.

However Umeda teaches a method wherein blood samples were collected from 149 glaucoma patients and 43 normal subjects. DNA was isolated from the blood samples and exons 4, 5, 6, and 16 of the OPTN gene were amplified by PCR. A heterozygous change 412G>A (Thr34Thr) in exon 4 was found in 18 POAG, 4 NTG, 4 SG, 2 CapG, 3 ConG, 3 PACG, and 6 normal patients (abstract). Thus Umeda teaches a method comprising determining the genotype of a sample with respect to the 412G>A polymorphism of the OPTN gene.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ishikawa by additionally determining the genotype of the sample with respect to the 412G>A polymorphism of the OPTN gene as suggested by Umeda. The prior art of Umeda teaches that the 412G>A polymorphism of the OPTN gene is also linked to glaucoma. As such one would be motivated to genotype for both of these mutations because early detection results in early treatment which can postpone or prevent loss of vision.

Ishikawa does not teach a method comprising determining the genotype of the sample with respect to the CGG to CAG substitution at codon 144 of the noelin 2 gene (Arg144Gln).

However Mukhopadhyay teaches that the noelin-2 should be tested as a candidate gene for eye disorders (such as POAG) since it is expressed in the eye and shares olfactomedin domains with MYOC (abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ishikawa by additionally determining the genotype of the sample with respect to the OPTN gene as suggested by Mukhopadhyay. Based on the teachings of Mukhopadhyay one of skill in the art would have been motivated to sequence all of the exons of OPTN gene looking for mutations that were associated with eye disorders. By sequencing each of the exons one would have determined the genotype of the sample with respect to the CGG to CAG substitution at codon 144 of the noelin 2 gene (Arg144Gln).

Conclusion

7. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634